(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/10125 A1

(51) International Patent Classification[7]: C07C 317/44, A61K 31/165

(21) International Application Number: PCT/US01/23689

(22) International Filing Date: 27 July 2001 (27.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/221,110	27 July 2000 (27.07.2000)	US
60/226,491	18 August 2000 (18.08.2000)	US
60/229,160	30 August 2000 (30.08.2000)	US
60/230,088	5 September 2000 (05.09.2000)	US
60/259,332	2 January 2001 (02.01.2001)	US

(71) Applicant *(for all designated States except BB, US)*: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 3190, Petah Tiqva 49131 (IL).

(71) Applicant *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SINGER, Claude** [IL/IL]; 8/8 David Elazar, Kfar Saba (IL). **GERSHON, Neomi** [IL/IL]; 11 Nachshon, Kfar Saba (IL). **CEAUSU, Arina** [IL/IL]; 2/26 Hakukia, Rishon Lezion (IL). **LIEBERMAN, Anita** [IL/IL]; 28 Ben Yosef, Ramat Aviv (IL). **ARONHIME, Judith** [IL/IL]; 9/7 Hava Lutzky, Rechovot (IL).

(74) Agents: **BRAINARD, Charles, R.** et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/10125 A1

(54) Title: CRYSTALLINE AND PURE MODAFINIL, AND PROCESS OF PREPARING THE SAME

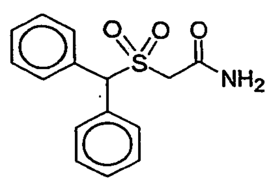
(57) Abstract: The present invention provides an improved process for preparing modafinil, whereby it may be isolated in high purity by a single crystallization. The process produces modafinil free of sulphone products of over-oxidation and other byproducts. The invention further provides new crystalline Forms II-VI of modafinil and processes for preparing them. Each of the new forms is differentiated by a unique powder X-ray diffraction pattern. The invention further provides pharmaceutical compositions containing novel modafinil Forms II-IV and VI.

peroxide in acetic acid. Example 1a of the '290 patent describes a different synthetic method for an industrial scale preparation of modafinil. Benzhydrol is reacted with thiourea to form an intermediate which is then hydrolyzed to 2-[(diphenylmethyl)thio]acetic acid. The acid is then oxidized *in situ* with hydrogen peroxide in a mixture containing chloroacetic acid and water. The resulting sulfoxide is then treated with dimethyl sulfate to methylate the carboxylic acid group. The resulting ester is derivatized with ammonia to modafinil.

Each of these methods uses hydrogen peroxide to oxidize a sulfide group to a sulfoxide. Drabowicz, J et al. *Synthesis*, 1990, 37-38 describes a procedure for oxidizing sterically hindered sulfides to sulfoxides. The procedure uses hydrogen peroxide as the oxidizing agent, methanol as the solvent and a mixture of sulfuric acid and one of several branched aliphatic alcohols as a catalyst. The procedure is well adapted for oxidizing sterically hindered sulfides. No products of over-oxidation were observed by thin layer chromatography of the reaction mixtures. Use of this methodology to prepare modafinil has not been described in the literature.

Sulfides also may be oxidized to sulfoxides with other oxidizing agents, such as sodium periodate, *t*-butyl hypochlorite, calcium hypochlorite, sodium chlorite, sodium hypochlorite, *meta*-chloroperbenzoic acid and sodium perborate. March J. *Advanced Organic Chemistry* 1201-02 (4th ed. 1992).

We have discovered that the process of Example 1 of the '290 patent suffers from a problem of over-oxidation of the sulfide to sulphone **2**.



2

By comparing the above presented chemical structures it will be readily appreciated that separation of the sulphone once formed from modafinil is a difficult task.

which have practical consequences in pharmacy. Crystalline forms of a compound are most readily distinguished by X-ray analysis. Single crystal X-ray crystalography yields data that can be used to determine the positions of the nuclei which in turn may be visualized with computer or mechanical models, thus providing a three-dimensional image of the compound. While single crystal X-ray studies provide unmatched structural information, they are expensive and quality data can sometimes be difficult to acquire. Powder X-ray diffraction spectroscopy is used more frequently by the pharmaceutical industry to characterize new crystalline forms of drugs than is single crystal X-ray analysis. Powder X-Ray diffraction spectroscopy yields a fingerprint that is unique to the crystalline form and is able distinguish it from the amorphous compound and all other crystalline forms of the compound.

There is a wide variety of techniques that have the potential of producing different crystalline forms of a compound. Examples include crystallization, crystal digestion, sublimation and thermal treatment. In the laboratory preparation in Example 1 of the '290 patent, modafinil is first precipitated by adding water to a reaction mixture containing modafinil, water and excess hydrogen peroxide. Modafinil is then recrystallized from methanol. In the industrial scale preparation of Example 1a, modafinil is obtained as a white powder by first crystallizing from a 1:4 mixture of methanol and water and then crystallizing again from a 1:9 methanol/water mixture. Crystallization from methanol and a 1:9 methanol/water mixture produces modafinil in polymorphic Form I. Modafinil Form I is characterized by a powder X-ray diffraction ("PXRD") pattern (Fig. 1) with reflections at 9.0, 10.2, 11.2, 12.9, 15.2, 15.8, 16.3, 17.7, 18.2, 19.3, 20.5, 21.6, 21.9, 23.2, 26.6±0.2 degrees 2θ.

U.S. Patent No. 4,927,855 describes the preparation of the levorotatory enantiomer of modafinil by chiral resolution of the 2-[(diphenylmethyl)sulfinyl]acetic acid with α-methylbenzyl amine. After recovery and amidation of the enantiomerically pure acid, (-) modafinil was obtained as white crystals by crystallization from ethanol.

The discovery of a new crystalline form of a pharmaceutically useful compound provides an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In this disclosure, modafinil with a combined impurity content of less than 0.1 % is referred to as "highly pure" modafinil. Purity is measured by UV absorbance at λ=225 nm. Compounds containing phenyl rings absorb strongly in this region of the U.V. spectrum. Modafinil and problematic impurities **2-4** each possess two phenyl UV chromophores. Modafinil that contains less than 0.01% of an impurity such as sulphone **2** is referred to as "essentially free" of that impurity and modafinil that is free of an impurity within the limit of detection of the purity analysis or that contains less than 0.0001% of the impurity is referred to as being "free" of that impurity.

The present invention provides an improved synthetic preparation of modafinil whereby modafinil may be isolated in ≥99.5 % purity after a single recrystallization, preferably ≥99.9% purity. In this improved process, 2-[(diphenylmethyl)thio]acetamide is oxidized to modafinil. The modafinil is then separated as a solid from the reagents used in the oxidation and thereafter is isolated in high purity by a single recrystallization.

In the oxidation step, hydrogen peroxide is reacted with 2-[(diphenylmethyl)thio] acetamide in the presence of a mineral acid and a linear, branched or cyclic alcohol, or a phase transfer catalyst, optionally in an inert liquid organic medium. The oxidizing conditions are discussed generally in Drabowicz, J et al. *Synthesis*, 1990, 37-38. U.S. Patent No. 4,177,290 is incorporated by reference for its teaching of a preparation of 2-[(diphenylmethyl)thio] acetamide.

Hydrogen peroxide is preferably supplied as a 10-50 wt. % solution in water, more preferably about 30-33 wt. % solution in water. Such solutions are commercially available (*e.g.* 1998-99 Aldrich Chemical Co. Cat. Nos. 42,065-4; 42,066-2; 31,698-9; 21,676-3).

Exemplary mineral acids that may be used include H_2SO_4, $HClO_4$ and H_3PO_4.

Preferred alcohols are derived from hydrocarbons with seven or fewer carbon atoms and that are unsubstituted except for the hydroxyl group. Branched alcohols are most preferred. Isopropyl alcohol, *tert*-butanol and 2-methyl-1-butanol are exemplary of alcohols that may be used. Suitable phase transfer catalysts include triethylbenzylammonium chloride (TEBA) and polyethylene glycol.

adding water. Modafinil is then separated from the reaction mixture by conventional means such as filtering or decanting. The modafinil preferably is then washed with an organic solvent and water.

The improved process for preparing modafinil produces modafinil with a low content of 2-[(diphenylmethyl)sulfonyl]acetamide **2**, 2-[(diphenyl methyl)sulphinyl] acetic acid **3**, and methyl 2-[(diphenylmethyl)sulphinyl] acetate **4**, which can be removed with a single recrystallization. The modafinil that precipitates from the reaction mixture should be 98-99% pure or greater and will typically contain less than 0.1 % suphone **2**. Modafinil has been precipitated directly from the reaction mixture with less than 0.01% contamination with sulphone **2**. The composition of the oxidation reaction mixture may be monitored quantitatively by HPLC to confirm that the reaction is proceeding cleanly. A reverse phase HPLC method with UV detection at λ=225 nm may be used.

Although modafinil obtained by oxidation according to the above-described process may be recrystallized from a variety of solvents in high purity, the best recrystallization solvents have been found to be methanol, ethanol, dimethylcarbonate, acetone, and mixtures thereof. The best multicomponent solvent systems are ethanol/dimethylcarbonate, acetone/dimethylcarbonate, acetone/water, acetone/ethyl acetate, acetone/dimethylcarbonate /water and methanol/dimethylcarbonate. An especially preferred recrystallization solvent is dimethyl carbonate.

The modafinil that is obtained after crystallization is ≥99.5% pure, more preferably ≥99.9% pure and contains less than 0.02%, more preferably less than 0.01% of of sulphone **2**. After crystallization from preferred recrystallization solvents, modafinil may be obtained free of sulphone **2**, *i.e.* with no more than 0.0002 % or 0.0001% contamination. It will be appreciated that such minute quantities of impurity are at or beyond the limits of detection of many analytical techniques.

In a second aspect, the present invention provides novel crystalline modafinil Forms II-VI and processes for their preparation.

A general technique that leads to the discovery of a novel crystalline form of a compound may be well known to those skilled in the art. In fact, that is commonly the case. Such techniques include crystallization, crystal digestion, sublimation, thermal

technique for preparing Form I by simply slurrying modafinil (in any other form) with ethyl acetate, isobutyl acetate or water until the conversion is complete.

Forms V and VI convert into modafinil Form I upon gentle heating to about 80°C or above. Forms V and VI may be transformed into Form I without significant decomposition by heating to about 100°C.

Modafinil Form I may be separated from solvents conventionally by filtering or decanting and then drying. Form I has been dried at a temperature as high as 100°C without converting to another crystalline or amorphous form and without undergoing significant chemical decomposition.

Modafinil Form II

The present invention also provides modafinil Form II. Modafinil Form II produces a powder X-ray diffraction pattern (Fig. 2) with reflections at 9.1, 10.3, 11.1, 11.9, 14.3, 15.2, 16.4, 17.5, 18.4, 20.5, 21.3, 24.6, 26.6±0.2 degrees 2θ. The strong reflections at 14.3, 17.5, 20.5 and 21.3 degrees 2θ are particularly characteristic. Of these, the reflections at 14.3, 17.5 and 21.3 degrees 2θ are most characteristic.

The following techniques have proven effective for producing modafinil in crystalline Form II.

Modafinil Form III converts into modafinil Form II when it is suspended in water. Thus, suspending Form III in water provides a method of accessing modafinil Form II.

Modafinil also crystallizes selectively in Form II from ethanol, isopropanol, *n*-butanol, *t*-butanol, methyl isobutyl ketone, ethylene glycol, dioxolane and dioxane by heating to dissolve modafinil in the solvent and cooling to recrystallize. Modafinil Form II also may be prepared by reslurrying in dichloroethane and by rapidly cooling a solution of modafinil in a methanol and water mixture.

Modafinil Form III

The present invention also provides modafinil Form III. Modafinil Form III produces a powder X-ray diffraction pattern (Fig. 3) with reflections at 7.4, 9.0, 10.5, 12.3, 14.2, 14.7, 15.1, 16.4, 18.3, 20.0, 20.5, 21.1, 22.1, 24.5±0.2 degrees 2θ.

Modafinil Form VI

The present invention also provides modafinil Form VI. Form VI produces a powder X-ray diffraction pattern (Fig. 6) with reflections at 9.0, 9.3, 10.2, 12.4, 14.2, 14.5, 15.3, 17.5, 18.1, 20.0, 20.5, 21.5, 22.0, 23.5, 24.5, 25.0±0.2 degrees 2θ. The reflections at 9.3, 18.1, and 20.5 degrees 2θ are particularly characteristic for their intensity.

Modafinil Form VI may be prepared by suspending modafinil Form V in water, ethanol or a water/ethanol mixture for a sufficient time to complete the conversion. Preferably, modafinil Form VI is slurried in water, ethanol, or an ethanol/water mixture at about 28°C, followed by drying under vacuum at 55°C.

Amorphous Modafinil

Modafinil may be prepared in an amorphous state by crystallization from mixtures of *ortho, meta or para* xylene.

Having described techniques best suited for producing distinct crystalline Forms II-VI of modafinil in a laboratory and industrial setting, those skilled in the art will appreciate that these forms may be accessible by yet other methods.

Pharamaceutical Compositions Containing Modafinil Forms II-IV and VI

Modafinil Forms II-IV and VI may be formulated into a variety of pharmaceutical compositions and dosage forms that are useful for promoting wakefulness in patients afflicted with narcopolepsy.

Pharmaceutical compositions of the present invention contain modafinil Forms II-IV and VI, optionally in mixture with each other. Pharmaceutical compositions of the present invention also may contain other modafinil crystalline forms, amorphous modafinil and/or other active ingredients in mixture with one or more of modafinil Forms II-IV and VI. In addition to the active ingredient(s), modafinil pharmaceutical compositions of the present invention may contain one or more excipients. Excipients are added to the composition for a variety of purposes.

When a dosage form such as a tablet is made by compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendancy to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid ethyl maltol, and tartaric acid.

Compositions may also be colored using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

Selection of excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and losenges as well as liquid syrups, suspensions and elixirs. An especially preferred dosage form of the present invention is a tablet.

Example 3: In a three necked round bottom flask equipped with reflux condenser, a thermometer, and an agitator, 3 g of modafinil prepared as in Example 1 was suspended in 32 ml acetone containing 5% water. The mixture was heated to reflux (~58 °C) under a nitrogen atmosphere. The solution so obtained was cooled to 42 °C at which temperature crystallization starts. The suspension was further cooled to 25 °C and filtered. After drying, 1.95 g of highly purified modafinil essentially free of sulphone was obtained (yield: 65%).

Example 4: In a three necked round bottom flask equipped with reflux condenser, a thermometer, and an agitator, 1 g of modafinil prepared as in Example 2 was suspended in 10.5 ml ethanol. The mixture was heated to reflux under nitrogen. The suspension was cooled to 25 °C and filtered. After drying 0.83 g of highly purified modafinil was obtained (yield: 83%).

Example 5: In a three necked round bottom flask equipped with reflux condenser, a thermometer and an agitator, diphenylmethylthio-2-acetamide (50 g)was suspended in dimethylcarbonate (550 ml). A solution (44 ml) containing 1.2 ml H_2SO_4 dissolved in 46.7 ml isopropanol was added. Further 49 ml of 30% H_2O_2 was added. The temperature increases to 30°C and was maintained constant during 8h. The reaction mass was cooled to 25 °C and diluted with 450 ml of water. The excess of unreacted H_2O_2 was neutralized with $Na_2S_2O_5$ and additional 50ml of water was added. Modafinil was separated by filtration and reslurried with 210 ml water. After drying 45.1g modafinil was obtained (yield 85%).

Example 6: In a three necked round bottom flask equipped with reflux condenser, a thermometer, and an agitator, 3 g of modafinil prepared as in Example 5 was suspended in a mixture containing 100 ml acetone and 20 ml dimethylcarbonate. Under nitrogen, the mixture was heated to reflux (~58 °C). The solution so obtained was cooled to 47 °C at which temperature crystallization starts. The suspension was further cooled to 25 °C and

Modafinil Forms V and VI were subsequently analyzed by x-ray powder diffraction and both were determined to be Form I.

Example 11: Crystallization from Acetonitrile. Modafinil (3 g) was suspended in acetonitrile (23 ml) in a three-necked round bottom flask equipped with a reflux condenser, a thermometer, and an agitator. The mixture was heated to reflux (about 80° C). The resulting solution was cooled to about 63° C at which point crystallization began. The suspension was furthered cooled to about 25° C and then filtered. After drying, crystallized modafinil (1.96 g) Form I was obtained (65% yield).

Example 12: Crystallization from Dimethylformamide. Modafinil (3 g) was suspended in dimethylformamide (5.5 ml) in a three-necked round bottom flask equipped with a reflux condenser, a thermometer, and an agitator. The mixture was heated to reflux (about 60° C). A clear solution was obtained. Water (5 ml) was added dropwise to the solution which caused modafinil to begin precipitating. Precipitation was completed by cooling the mixture to about 25° C. The product was separated by filtration. After drying, crystallized modafinil (2.54 g) Form I was obtained (84.7% yield).

Example 13: Crystallization from Ethyl Acetate. Modafinil (3 g) was suspended in ethyl acetate (50 ml) in a three-necked round bottom flask equipped with a reflux condenser, a thermometer, and an agitator, . The mixture was heated to reflux (about 77° C) and maintained for about 1 hour. The mixture was cooled to about 25° C and then was filtered. After drying, crystallized modafinil Form I (1.9 g) was obtained (63% yield).

EXAMPLES 14-15

(Preparation of Modafinil Form II)

Example 14: Crystallization from Isopropanol. Modafinil (3 g) was suspended in isopropanol (34 ml) in a three-necked round bottom flask equipped with a reflux condenser, a thermometer, and an agitator. The mixture was heated to reflux (about 85° C). The resulting solution was cooled to about 58° C at which point crystallization began.

EXAMPLE 18

(Preparation of Modafinil Form V)

Example 18: Crystallization from Dimethylcarbonate. Modafinil (3 g) was suspended in dimethylcarbonate (105 ml). The mixture was heated to reflux (about 90° C) in a three-necked round bottom flask equipped with a reflux condenser, a thermometer, and an agitator. After about 2 hours at reflux, the resulting solution was cooled to about 79° C at which point crystallization began. The suspension was cooled to about 25° C and then was filtered. After drying, about crystallized modafinil (3 g) Form V was obtained (about 90% yield).

EXAMPLE 19

(Preparation of Modafinil Form VI)

Example 19: From a Suspension of Form V in Ethanol. Modafinil (3.5 g) Form V was suspended in ethanol (10 ml) in a three-necked round bottom flask equipped with a descending condenser, a thermometer, and an agitator. The mixture was stirred for about 4.5 hours at about 25° C and then was filtered. After drying, crystallized modafinil (2.9 g) Form VI was obtained (82% yield).

EXAMPLE 20

(Preparation of Amorphous Modafinil)

Example 20: Crystallization from Xylenes. Modafinil (5 g) was suspended in of xylene (150 ml) in a three-necked round bottom flask equipped with a descending condenser, a thermometer and an agitator . The mixture was heated to about 110° C, which was maintained for about 30 minutes. The resulting solution was cooled to about 35° C at which point crystallization began. The suspension was maintained for about 17 hours at about 25° C, then cooled to about 5° C, and then was filtered. After drying, amorphous modafinil (1.83 g) was obtained (36.6% yield).

Having thus described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification and examples. It is intended that the specification,

CLAIMS

We claim:

1. A process for preparing modafinil comprising the steps of:
   a) oxidizing 2-[(diphenylmethyl)thio]acetamide with H_2O_2 in a mixture of a mineral acid with an alcohol or phase transfer catalyst,
   b) precipitating a solid containing modafinil from the mixture, and
   c) separating the mixture from the precipitated solid.
2. The process of claim 1 further comprising isolating modafinil in purity greater than or equal to 99.5% from the precipitated solid by a single crystallization.
3. The process of claim 2 wherein the modafinil is isolated in purity greater than or equal to 99.9% from the precipitated solid by a single recrystallization.
4. The process of claim 1 wherein the modafinil is isolated in pharmaceutically acceptable purity.
5. The process of claim 1 wherein the purity of the modafinil is measured by the relative area of peaks in a chromatogram obtained by ultraviolet detection using 225 nm wavelength light.
6. The process of claim 1 wherein the precipitated solid is modafinil in greater than or equal to 99 % purity.
7. The process of claim 6 wherein the precipitated solid is modafinil in greater than or equal to 99.5 % purity.
8. The process of claim 1 wherein the H_2O_2 is added to the mixture as a 10-50 weight percent solution in water.
9. The process of claim 1 wherein the mineral acid is selected from the group consisting of sulfuric acid, perchloric acid, and phosphoric acid.
10. The process of claim 1 wherein the alcohol is selected from the group consisting of isopropanol, *tert*-butanol, and 2-methyl-1-butanol.
11. The process of claim 1 wherein the mixture further includes an inert liquid organic medium.

a) suspending crystalline Form II modafinil in a liquid selected from the group consisting of methyl *t*-butyl ether, water, isobutyl acetate and mixtures thereof for a period of time sufficient to convert the Form II modafinil into modafinil Form I, and

b) separating the liquid to obtain modafinil Form I.

25. A process for preparing modafinil Form I by heating Form V modafinil to about 80°C or higher temperature for a period of time sufficient to convert the Form V modafinil into Form I modafinil.

26. A process for preparing modafinil Form I by heating Form VI modafinil to about 80°C or higher temperature for a period of time sufficient to convert the Form V modafinil into modafinil Form I.

27. A crystalline form of modafinil that produces a powder X-ray diffraction pattern with reflections at 14.3, 17.5, 20.5 and 21.3±0.2 degrees 2θ.

28. The crystalline modafinil of claim 27 denominated modafinil Form II.

29. The crystalline form of modafinil of claim 27 wherein the reflections at 14.3, 17.5, 20.5 and 21.3±0.2 degrees 2θ comprise a first set of reflections of strong intensity and wherein the crystalline form is further characterized by reflections of lesser intensity at 9.1, 10.3, 11.9, 15.2, 18.4, 24.6 and 26.6±0.2 degrees 2θ.

30. The crystalline form of modafinil of claim 27 that produces a powder X-ray diffraction pattern with reflections at 9.1, 10.3, 11.1, 11.9, 14.3, 15.2, 16.4, 17.5, 18.4, 20.5, 21.3, 24.6, 26.6±0.2 degrees 2θ.

31. A process for preparing the modafinil of claim 27 comprising the steps of:

a) suspending Form III modafinil in water for a period of time sufficient to convert Form III modafinil into the modafinil of claim 27, and

b) separating the water to obtain the modafinil of claim 27.

32. A process for preparing the modafinil of claim 27 comprising the steps of:

a) dissolving modafinil in a liquid selected from the group consisting of ethanol, isopropanol, *n*-butanol, *t*-butanol, methyl isobutyl ketone, ethylene glycol, dioxolane, dioxane and mixtures thereof,

b) crystallizing modafinil from the liquid, and

c) separating the liquid to obtain the modafinil of claim 38.

43. A crystalline hemisolvate of modafinil and dimethylcarbonate.

44. The crystalline hemisolvate of modafinil and dimethylcarbonate of claim 43 that produces a powder X-ray diffraction pattern with reflections at 9.3, 12.4, 18.2, 19.9 and 22.0±0.2 degrees 2θ.

45. The crystalline hemisolvate of modafinil and dimethylcarbonate of claim 43 denominated modafinil Form V.

46. The crystalline form of modafinil of claim 44 wherein the reflections at 9.3, 12.4, 18.2, 19.9 and 22.0±0.2 degrees 2θ comprise a first set of reflections of strong intensity and wherein the crystalline form is further characterized by reflections of lesser intensity at 7.4, 24.7, 26.2, 21.5, 23.6, 24.5 and 25.2±0.2 degrees 2θ.

47. The crystalline form of modafinil of claim 46 that produces a powder X-ray diffraction pattern with reflections at 7.4, 9.3, 10.5, 12.4, 14.7, 16.2, 18.2, 19.9, 21.5, 22.0, 23.6, 24.5, 25.2, 28.4, 29.5, 31.8±0.2 degrees 2θ.

48. A process for preparing the modafinil of claim 43 comprising the steps of:
   a) dissolving modafinil in liquid selected from the group consisting of methylcarbonate, ethanol and dimethylcarbonate mixtures, water and dimethylcarbonate mixtures and acetone and dimethylcarbonate mixtures
   b) crystallizing modafinil from the liquid, and
   c) separating the liquid to obtain the modafinil of claim 43.

49. A crystalline form of modafinil that produces a powder X-ray diffraction pattern with reflections at 9.3, 18.2, and 20.5±0.2 degrees 2θ.

50. The crystalline modafinil of claim 49 denominated modafinil Form VI.

51. The crystalline form of modafinil of claim 49 wherein the reflections at 9.3, 18.2, and 20.5±0.2 degrees 2θ comprise a first set of reflections of strong intensity and wherein the crystalline form is further characterized by reflections of lesser intensity at 9.0, 10.2, 12.4, 15.3, and 20.0±0.2 degrees 2θ.

52. The crystalline form of modafinil of claim 51 that produces a powder X-ray diffraction pattern with reflections at 9.0, 9.3, 10.2, 12.4, 14.2, 14.5, 15.3, 17.5, 18.1, 20.0, 20.5, 21.5, 22.0, 23.5, 24.5, 25.0±0.2 degrees 2θ.

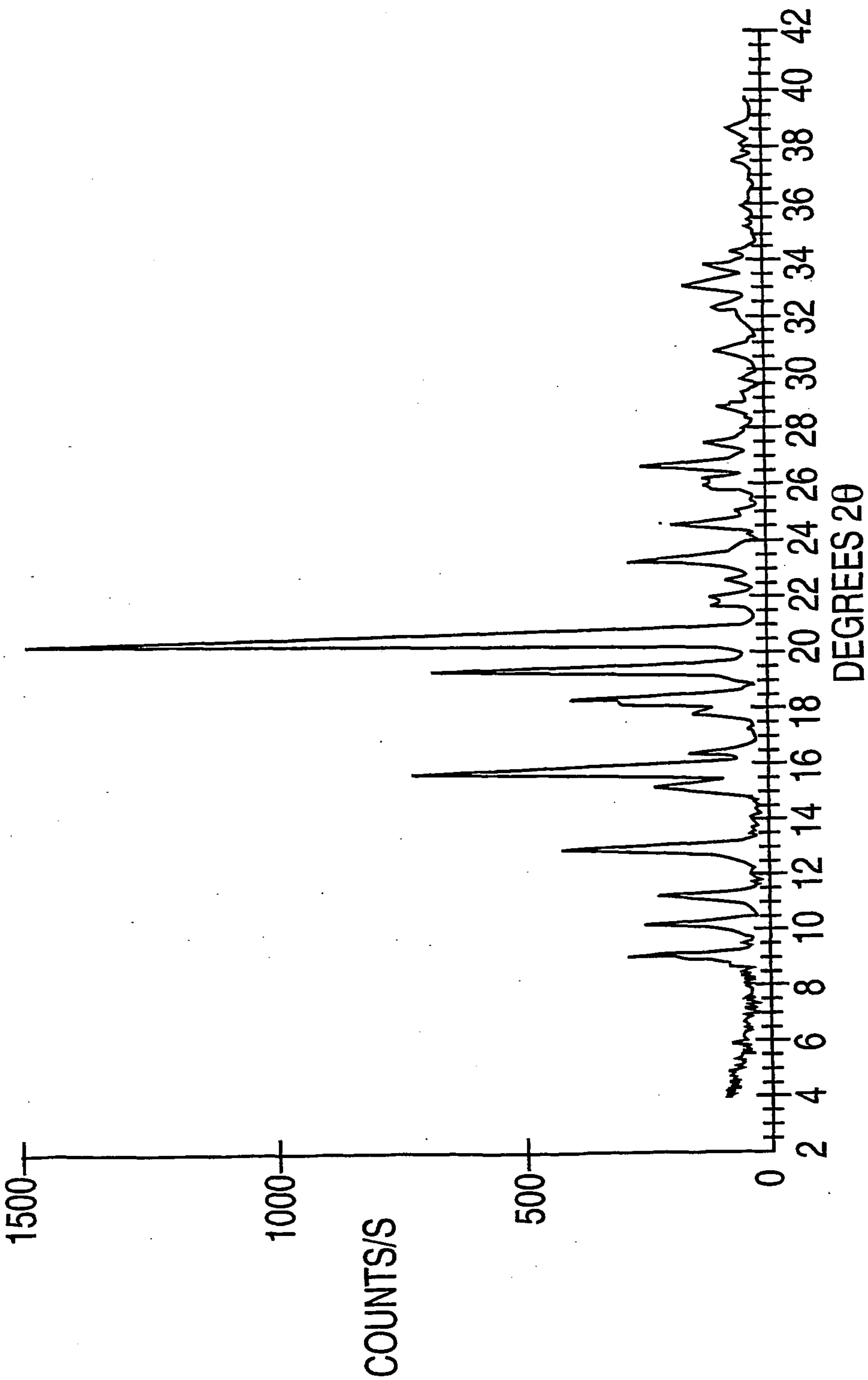

COUNTS/S
1500
1000
500
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
DEGREES 2θ

FIG.1

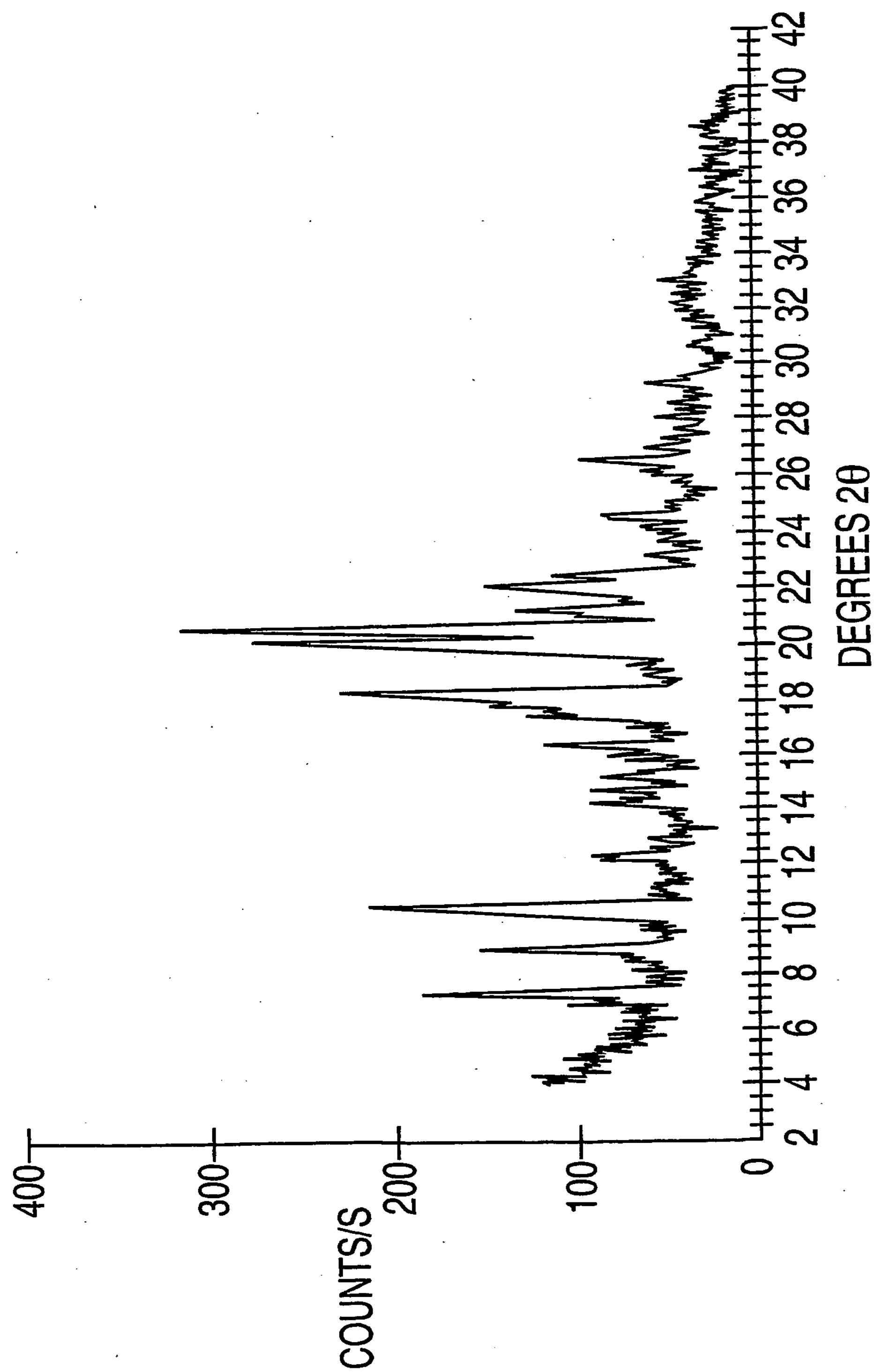

COUNTS/S
400
300
200
100
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
DEGREES 2θ

FIG. 3

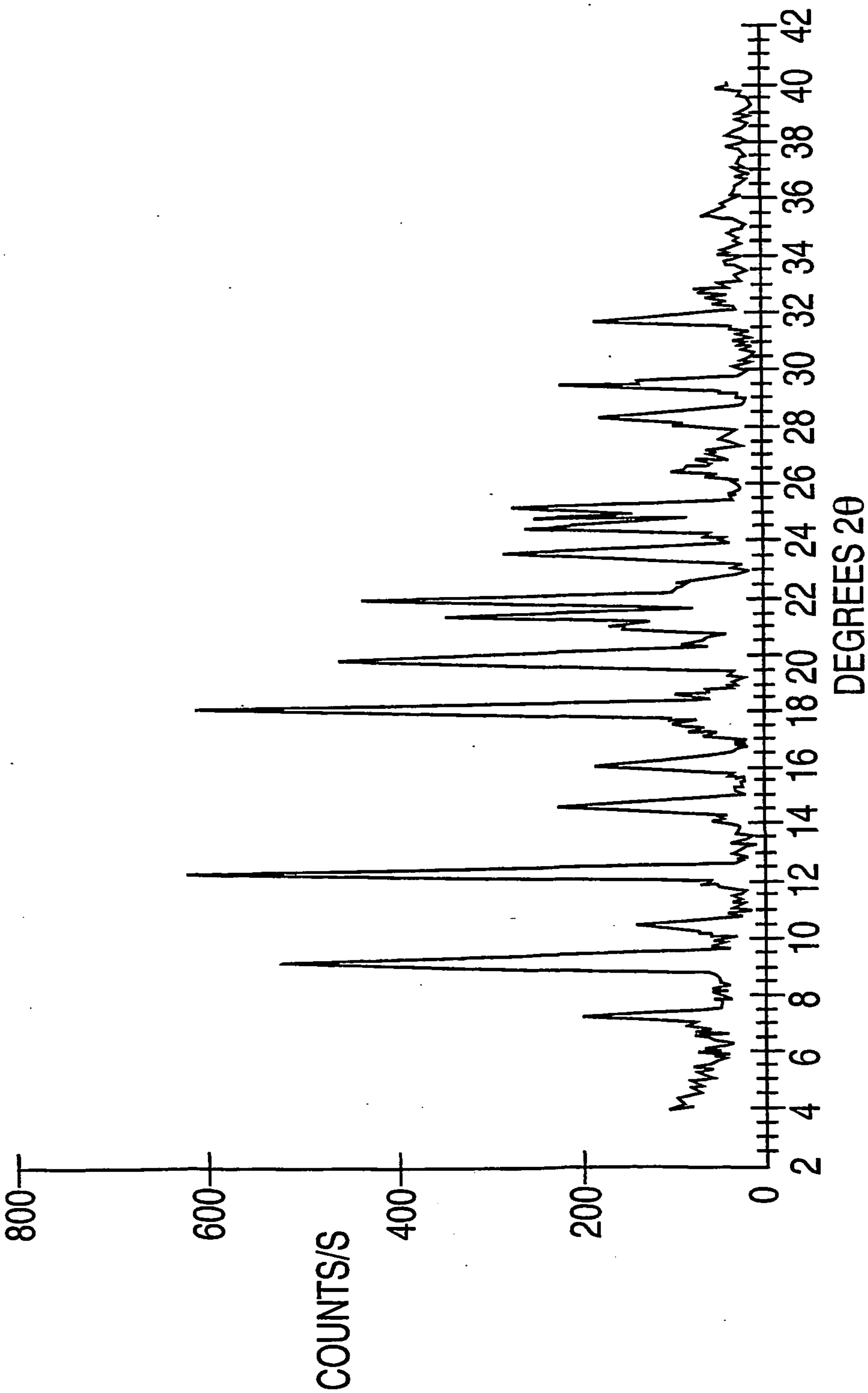

COUNTS/S
0
200
400
600
800
DEGREES 2θ
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/23689

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07C 317/44; A61K 31/165
US CL :564/162; 514/618
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/162; 514/618

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
WEST

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CASONLINE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,719,168 A (LAURENT) 17 February 1998, col. 3, lines 60-67, claim 1, 5.	1-61
Y	US 4,177,290 A (LAFON) 04 December 1979, col 3, lines 30-36, and col. 1, lines 25-45.	1-61
Y	DRABOWICZ, J. et al A Convenient Procedure for the Oxidation of Sterically hindered sulfides to Sulfoxides. Synthesis. October 1990, pages 937-938, especially, page 937, column 1.	1-61

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 SEPTEMBER 2001	15 NOV 2001

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Joyce Bridgers for SHAILENDRA KUMAR
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235